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(54) Title: MICROEMULSIONS FOR USE AS VEHICLES FOR ADMINISTRATION OF ACTIVE COMPOUNDS

(57) Abstract

A non-toxic oil-in-water or bicontinuous microemulsion as a vehicle for administration of one or more active compounds having a low solubility in water, which microemulsion contains: a polar phase containing water and optionally an agent for obtaining isotonic conditions, and one or more components (modifiers) for adjusting the polarity of the polar phase; a surfactant film modifier; a non-polar phase consisting of at least one pharmaceutically acceptable oil; and a mixture of a hydrophilic surfactant and a hydrophobic surfactant up to 15 % by weight of the total microemulsion, wherein the hydrophobic surfactant is chosen from a group consisting of lecithin, sphingolipids or galacto lipids.

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MICROEMULSIONS FOR USE AS VEHICLES FOR ADMINISTRATION OF ACTIVE COMPOUNDS

Technical field

The present invention relates to a microemulsion used as a pharmaceutically acceptable vehicle for administration of one or more active compounds parenterally but also orally and transdermally, as well as a process for the preparation and use of such a microemulsion.

The object of the present invention is to provide a vehicle which increases the solubility of compounds having a low solubility in water at the same time as being non-toxic.

Background of the invention and prior art

Many of the new pharmaceutically active substances which are prepared today have a very low solubility in water. This could be a problem when administered, especially when a substance is to be administered parenterally, e.g. intravenously, intraperitonially, intraarterially, intramuscularly or subcutaneously. In these cases a vehicle which increases the solubility of the active compound is needed. The solubility in water often has to be increased 1000 times to 10 000 times to reach reasonable volumes for administration. The systems used today are;

- solvents which are possible to mix with water, such as propylene glycol, polyethylene glycol, ethanol e.t.c;
- surfactants forming aggregate in which the unsoluble substances can be dissolved, for example ethoxylated castor oil, mixed micells of lecithin + bile salts;
- polyethylene oxide derivatives of sorbitan monoesters, diesters and triesters;
- complexing agents such as cyclodextrines;
- emulsions, for example soybean oil + egglecithin.

All these systems have different drawbacks. Solvents which are possible to mix with water require high concentrations to be effective. The solubilizing capacity of the surfactants and the complexing agent is often insufficient. Emulsions are thermodynamically unstable and also nontransparent which makes it difficult to decide whether the active substance is completely dissolved or not. Microemulsions are on the contrary, thermodynamically stable mixtures that are formed spontaneously without any addition of external energy, e.g. mecanical stirring, heating, ultrasonification e.t.c. Microemulsions are also transparent which make them superior to ordinary emulsions for use as vehicles for administration of pharmacetically active compounds.

One objective with the present invention is to provide a microemulsion using minimal amounts of surfactants for use as a vehicle suitable for parenteral as well as oral and transdermal administration of one or more pharmaceutically active compounds.

The benefit with a microemulsion is the high solubilization capacity and the fact that it is both thermodynamically stable and translucent. In EP 211 258 a preparation called an "oil-in-water microemulsion" for parenteral administration is described, which consists of pharmaceutically acceptable lipids, lipophilic drugs and mixtures thereof, and a phospholipid emulsifier in an aqueous phase. However, here the microemulsification is achieved by using mechanical energy input, i.e. droplet size reduction via microfluidization. This is not a microemulsion according to usual definition for microemulsions - "a microemulsion is defined as a system of water, oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution" (Danielsson, I., Lindman, B., Colloids and Surfaces, 1981, 3, p. 391). An oil-in-water microemulsion for parenteral administration is described in FR 2 553 661. This microemulsion contains an ionic surfactant and a aliphatic polyol or an aromatic alcohol having at least 4 carbon atoms as a co-surfactant. In the example of this specification the ratio lipophilic phase : surfactant is 1 : 1. In WO 92/18147 a water-in-oil microemulsion is described which readily converts to an oil-in-water emulsion or microemulsion by the addition of aqueous fluid. This microemulsion contains a hydrophilic water-soluble active

substance. However, it is most likely impossible to use as low amount of surfactant as stated in the claims since there is a need for some kind of surfactant modifier to lower the amount of surfactant. Furthermore, US 4 712 239 describes multicomponent systems for use in pharmaceutical products, which systems comprising an oil, a nonionic surfactant with a hydrophilic-lipophilic balance above 8 and a cosurfactant which is a partial ether or ester of a polyhydroxyl alcohol and a (C_{6-22})fatty alcohol or acid. Optionally an aqueous phase is used and the therapeutic agent may be lipophilic or hydrophilic. Such systems are said to give enhanced transdermal delivery characteristics. In example 1, formulations X and XI contain isopropanol which make the formulations inappropriate for parenteral administration. Furthermore, it is to be noted that in example 1, formulation I the ratio of the medium-chain triglyceride to the caprylic-capric acid glycerol partial esters is 1:1.5. Also WO 93/02664 describes a microemulsion but it is in the form of a water-in-oil microemulsion. Among others it includes a water-soluble therapeutic agent. In EP 334 777 a microemulsion for parenteral or oral administration of cosmetics or pharmaceuticals is disclosed consisting of one polar and one lipid phase and using a mixture of surfactants based upon polyethylene glycol and polyglycerol. The amount of surfactants has to be above 15 % by weight in order to achieve a microemulsion according to the definition above.

None of the prior art documents discloses a non-toxic microemulsion suitable for parenteral administration of substances having a low solubility in water, which microemulsion could be either in form of a oil-in-water microemulsion or a bicontinous microemulsion and also is easy to prepare. Thus, there is a need for a new vehicle having the above listed characteristics.

Brief description of the invention

The object of the present invention is to provide a pharmaceutically acceptable non-toxic vehicle which increases the solubility of compounds having a low solubility in water, and which vehicle is in form of a microemulsion which is stable, translucent and suitable for parenteral as well as oral and transdermal administration of one or more active compounds.

The microemulsion is defined in claim 1 and further preferred embodiments of the invention are disclosed in claims 2-18.

Detailed description of the invention

According to the present invention a microemulsion which is suitable for parenteral as well as oral and transdermal administration of one or more active compounds is disclosed. It has surprisingly been found that by using at least two types of modifiers it is possible to minimize the amount of the surfactant and thus, also the toxicity is minimized.

The present microemulsion comprises
- a polar phase containing water and optionally an agent for obtaining isotonic conditions, and one or more components (modifiers) for adjusting the polarity,
- a surfactant film modifier,
- a non-polar phase consisting of at least one pharmaceutically acceptable oil and
- a mixture of a hydrophilic and a hydrophobic surfactant up to 15% by weight of the total microemulsion, preferably 4-12%.

The polar phase includes water and optionally an agent for obtaining isotonic conditions, e.g a NaCl- or glycerol solution. The polar phase also includes compound/compounds which decrease the polarity of the polar phase and thus, lowering the amount of surfactant. These compounds are called modifiers. Examples of modifiers are; polyethylene glycol 400 (PEG 400), polyethylene glycol 300 (PEG 300), polyethylene glycol 200 (PEG 200); propylene glycol; glucofurol (polyethyleneglycol tetrahydrofurfurylether); glycerol; sorbitol; mannitol; monosaccharides; disaccarides; dimethyl acetamide; solketal;

methylpyrrolidone; 1-hydroxyethyl-2-pyrrolidon or hydroxyethyl lactamide. Preferred modifiers are one or more of the following; polyethylene glycol 400 (PEG 400), polyethylene glycol 300 (PEG 300), polyethylene glycol 200 (PEG 200); propylene glycol; glucofurol; glycerol; sorbitol; mannitol; monosaccharides or disaccarides. More preferred modifiers are one or more of the following; polyethylene glycol 400 (PEG 400), polyethylene glycol 300 (PEG 300), polyethylene glycol 200 (PEG 200); propylene glycol; glucofurol and glycerol. Most preferred modifier is the compound PEG 400.

The surfactant film modifier will be partially incorporated in the polar part of the surfactant film, thereby both increasing the area per lipid polar head group, and thus changing the spontaneous curvature of the lipid layers from being slightly curved toward water to become more planar or curved toward oil, and decreasing the stability of the lamellar liquid crystalline phase. Preferably the surfactant film modifier is ethanol, but also C_3-alcohols might be useful in case of transdermal administration.

The non-polar phase consists of at least one pharmaceutically acceptable oil which may be a triglyceride containing fatty acids having 4-18 carbon atoms; a diester of propylene glycol containing fatty acids having 4-18 carbon atoms; a monoester of a fatty acid containing an alcoholic part consisting of 1-5 carbon atoms and a fatty acid part having 8-22 carbon atoms or mixtures thereof.

Preferably the non-polar phase consists of a triglyceride containing at least 70 % of fatty acids having 8-10 carbon atoms; a diester of propylene glycol containing at least 70 % of fatty acids having 8-10 carbon atoms; or of a monoester of a fatty acid such as isopropylmyristate, isopropylpalmitate or ethyloleate or mixtures thereof. More preferred the non-polar phase consists of a triglyceride containing at least 70 % of fatty acids having 8-10 carbon atoms; a diester of propylene glycol containing at least 70 % of fatty acids having 8-10 carbon atoms or of isopropylmyristate. Most preferred the non-polar phase consists of either a triglyceride containing at least 70 % of fatty acids having 8-10 carbon atoms or isopropylmyristate.

The hydrophobic surfactant is one of lecithin, sphingolipids and galacto lipids. Most preferred hydrofobic surfactant is purified soybean lecithin, comprising at least 90 % phosphatidyl cholin. The non-ionic hydrophilic surfactant could be ethoxylated castor oil; ethoxylated fatty esters; sucrose fatty esters; mono-, di- and triesters of sorbitol and sorbitan and polyoxyethylene derivatives thereof; alkyl glucosides or alkyl polyglucosides; ethoxylated mono-hydroxy stearic acid and bile salts. Preferably the hydrophilic surfactant is polyethylene glycol (15)-12-hydroxy stearate, an alkylmaltoside, bile salts or mixtures thereof.

The present invention provides both an oil-in-water microemulsion and a bicontinous emulsion. By changing the ratio between the polar and the non-polar phase and also the amount of the modifiers mixed with the water in the polar phase, it is possible to obtain a microemulsion either in an oil-in-water type or bicontinous type. The microemulsion according to present invention may be used for solubilizing active compounds for intravenous, intraperitonial or intraarterial administration. It may also be used for preparations of active compounds having a low solubility in water for subcutaneous, intramuscular or transdermal administration. A further use of the microemulsion could be solubilization and increased absorption of active compounds having a low solubility in water when administed orally.

The active compound could e.g. be a proton pump inhibitor, calcium channel blocker, beta blocker, anesthetic, steroid, antioxidant, renin inhibitor, alkaloid, cytostatica, anti-coagulant, lipid regulating agent, anti-depressant, neuroleptic, immunosuppressant, immunomodulator, antibiotic, anti-inflammatory agent.

Preparation

The microemulsion could be prepared by mixing the components together in no particular order and allow the mixture to equilibrate typically two or three days. The equilibrating procedure could be shortened by gentle heating of the mixture to about 40°C, and stirring or shaking the mixture at regular intervals. It should be noted that the optimum concentration of the modifiers may have to be optimized for different batches of soybean lecithin and also for different active compounds.

The invention is illustrated more in detail by the following examples.

Example 1

The following components were mixed together in a glass vial:

1a

Component	Composition	Amount (g)	wt%
Surfactants	Epicuron 200[1]	0.28	7.0
	Soluthol HS15[2]	0.196	4.9
Aq-phase	water	1.11	27.8
	PEG 400[3]	0.456	11.4
	ethanol (99.5%)	0.196	4.9
oil phase	Miglyol 810[4]	1.76	44.0

1b

Component	Composition	Amount (g)	wt%
Surfactants	Epicuron 200[1]	0.7	7.0
	Soluthol HS15[2]	0.49	4.9

Component	Composition	Amount (g)	wt%
Aq-phase	water	1.66	16.6
	PEG 400[3]	0.685	6.85
	ethanol (99.5%)	0.293	2.93
oil phase	Miglyol 810[4]	6.17	61.7

1c

Component	Composition	Amount (g)	wt%
Surfactants	Epicuron 200[1]	0.28	7.0
	Soluthol HS15[2]	0.196	4.9
Aq-phase	0.9 % NaCl	1.11	27.8
	PEG 400[3]	0.456	11.4
	ethanol (99.5%)	0.196	4.9
oil phase	Miglyol 810[4]	1.76	44.0

1d

Component	Composition	Amount (g)	wt%
Surfactants	Epicuron 200[1]	0.70	7.0
	Soluthol HS15[2]	0.49	4.9
Aq-phase	0.9 % NaCl	1.66	16.6
	PEG 400[3]	0.685	6.85

Component	Composition	Amount (g)	wt%
	ethanol (99.5%)	0.293	2.93
oil phase	Miglyol 810[4]	6.17	61.7

[1]Epicuron 200 is a purified soybean lecithin manufactured by Lucas Meyer, Germany.

[2]Soluthol HS15 is a polyoxyethylene glycol(15)-12-hydroxy stearat manufactured by BASF, Germany.

[3]PEG 400 is polyethylene glycol with the average molecular weigth of 400 g/mole.

[4]Miglyol 810 is a triglyceride with the chainlength distribution of the fatty acids according to the manufacturer: $C_{6:0}$ = 2% max, $C_{8:0}$ = 70-80%, $C_{10:0}$ = 18-28%, $C_{12:0}$ = 2% max.

The glass vial was sealed and the mixture was shaken using a vortex mixer for a given number of minutes and then kept in a water bath keeping a constant temperature of 37°C for two days. The vial was shaken using the vortex mixer two or three times a day. After two days the mixture appeared as a transparent slightly viscous one phase liquid. The mixture was kept at 25°C for one week and showed no sign of phase separation. The sample was tested by visual appearance and using cross polarized filters to detect any sign of liquid crystalline phases.The temperature was raised to 37°C and the sample was inspected after two days using the same procedure without any sign of phase separation. The sample was then kept in room temperature and inspected at regular intervals and the stability was at least six months.

Example 2

The following components were mixed together in a glass vial:

2a:

Component	Composition	Amount (g)	wt%
Surfactants	Epicuron 200	0.120	3.0
	Solutol HS15	0.240	6.0
Aq-phase	water	1.274	31.8
	PEG 400	0.385	9.6
	ethanol	0.165	4.1
Oil phase	isopropylmyristate	1.828	45.6

2b:

Component	Composition	Amount (g)	wt%
Surfactants	Epicuron 200	2.8	2.8
	dodecylmaltocid	1.2	1.2
Aq-phase	water	38.17	38.17
	glucose	9.58	9.58
	ethanol	10.08	10.08
Oil phase	isopropylmyristate	38.17	38.17

2c:

Component	Composition	Amount (g)	wt%
Surfactants	Epicuron 200	4.9	4.9
	dodecylmaltocid	2.1	2.1

Component	Composition	Amount (g)	wt%
Aq-phase	water	35	35
	glucose	10	10
	ethanol	13	13
Oil phase	isopropylmyristate	35	35

2d:

Component	Composition	Amount (g)	wt%
Surfactants	Epicuron 200	6.5	6.5
	Na-taurocholate	1.0	1.0
Aq-phase	water	39.25	39.25
	PEG 400	7.0	7.0
	ethanol	7.0	7.0
Oil phase	isopropylmyristate	39.25	39.25

2e:

Component	Composition	Amount (g)	wt%
Surfactants	Epicuron 200	6.5	6.5
	Na-taurocholate	1.0	1.0
Aq-phase	water	38.75	38.75

Component	Composition	Amount (g)	wt%
	ethanol	7.0	7.0
Oil phase	isopropylmyristate	39.25	39.25

The mixture was equilibrated according to the process in example 1, and after two days the mixture appeared as a transparent slightly viscous one phase liquid. The mixture was kept at 25°C for one week and showed no sign of phase separation. The sample was tested by visual apperance and using cross polarized filters to detect any sign of liquid crystalline phases.The temperature was raised to 37°C and the sample was inspected after two days using the same procedure without any sign of phase separation.

Example 3

A microemulsion according to example 1 was prepared and the solubility of two sparingly soluble substances, felodipine (ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate) and cis-4b,5,9b,10-tetrahydro-4b,7,9,9b-tetramethyl-8-ethoxy-indeno(1,2-b)indole, hereinafter called the indeno indole, were tested. Different amounts of the substances were added to 1 ml samples of the microemulsion placed in glass vials. The samples were rotated for 48 hours to allow a complete wetting of the solid substance. The samples were than kept in a waterbath at 25°C for at least one week before inspection. The samples were inspected for any solid substance or phase separation and the maximum solubility was defined as the range between the last sample in each serie without any trace of solids or phase separation, and the first sample with remaining and undissolved substance or a phase separation.

Table 1. Solubility of felodipine and the indeno indole in a microemulsion prepared according to example 1.

	Sol. in water mg/l	sol. in microemulsion 1a mg/l	sol. in microemulsion 1b mg/l
Felodipine	0.8	5000-10000	10 000-15 000
The indeno indole	2.0	40 000-50 000	60 000-75 000

Example 4

The effect of a microemulsion according to example 1a on different pharmacological parameters in consious rats was compared with a 50 % PEG 400/water solution using saline as a control.

Biological effect

Experimental procedure and material

Animals

Adult, male Sprague-Dawley rats from Denmark, were used. After arrival at Astra Hässle AB, the animals were allowed at least one week to acclimatise before surgery. They were maintained in standard rat cages with aspen-chip bedding in a room with regulated temperature (20 - 22 °C), humidity (50 - 70 %) and with a 12/12 h light/dark cycle. The animals had free access to pellets and to tap-water from bottles.

Surgery

The day before the experiments, the animals were anesthetised with Methohexital Sodium (Brietal, Lilly, Indianapolis, Ind, USA) 60 mg/kg i.p. and catheters were inserted in the right jugular vein (PE 25 for i.v. drug injections) and the tail artery (8 cm long PE 10 connected to PE 90 for blood pressure recordings). The tip of the arterial catheter was placed in the abdominal aorta below the renal arteries. ECG electrodes were placed under the skin over the apex and the right shoulder, and the ground electrodes were placed over the lumbar spine. This corresponds to a CR-recording. After the surgical

procedure the animal was placed alone in a cage in a room with regulated humidity, temperature and light/dark cycle. The rats were also connected to a swivel system (Carnegie, Stockholm, Sweden), which delivered 1.0 ml sterile saline per hour via the arterial pressure line.

Hemodynamic and ECG recordings:

The day after the acute surgical procedure, the experiments were performed with the conscious rat residing in its own cage. The tail artery catheter was connected via a swivel allowing the animal to move relatively freely. The arterial pressure catheter was connected to a pressure transducer. The catheter was kept patent by slow infusion of 1.0 ml NaCl/h via a side tube of the arterial pressure line. The side tube was a 60 cm long PE 10 catheter, which has a high internal resistance. Thus, the side tube does not damp out arterial pulsations. Heart rate (HR) was measured from the undamped arterial pressure signal with a rate meter, and mean arterial pressure (MAP) was obtained by electronic filtering. The parameters from 4 animals were displayed simultaneously on a Grass polygraph (model 7 D). The ECG electrodes were connected intermittently to a Grass (7P6) ECG pre-amplifier. The ECG was recorded on a calibrated Siemens Elema Inkjet recorder.

The mean arterial pressure and heart rate signals were fed into a Datatranslation (DT 2801) AD converter placed in a Compaq 386SX computer. The computer program PC-LAB (written by Jan Axenborg and Ika Hirsch, AB Astra Hässle) sampled values of arterial pressure and heart rate repeatedly during the course of the experiments. The program sampled arterial pressure and heart rate for 20 s and calculated the average values of each 20 s period once every minute during the 4.5 h of experiments (i.e. created a file with 285 values of the individual parameters from 3-4 rats simultaneously).

In addition, the PC-LAB program sampled the ECG from all 4 rats 8 times during the course of the experiment (see Fig. 1). ECG signals were sampled at 800 Hz for 4 s, i.e.

about 20 ECG cycles from each rat were stored in the computer memory. This array of samples from 4 rats was then transferred to a VAX-computer at AB Astra Hässle and was analysed with the PC-LAB program (written by Jan Axenborg). The PC-LAB. program calculated an average ECG from about 20 cycles. The 2nd cycle is the triggering cycle and is used for all calculations. From the average ECG, we calculated the PQ-time and QRS-duration in milliseconds.

Experimental procedures

The experimental procedure is illustrated in Fig. 1. The experiment was performed on 3 different vehicles.

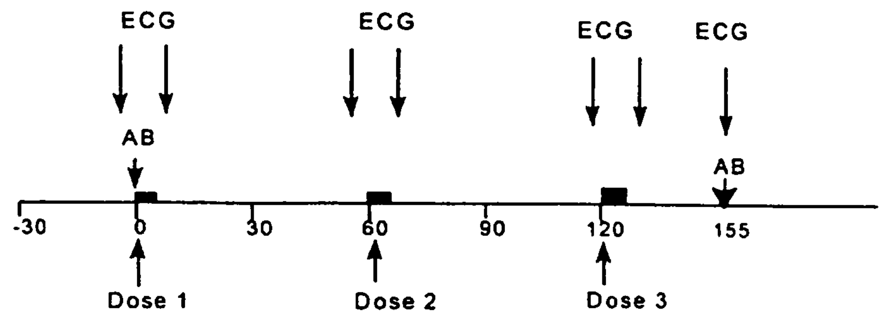
The basic hemodynamic parameters were recorded for 30 min. (see Fig. 1). Then the animals received 3 infusions of the vehicle given during 5 min. The volume was 0.3, 1 and 3 ml/kg for saline and PEG 400 and 0.15, 0.5 and 1.5 ml/kg for the microemulsion. The infusions were given 60 min. apart.

Blood samples for acid-base balance and blood gas determinations were obtained twice (before the first dose and at the end of the experiment).

ECG was obtained at intervals shown in Fig 1.

Fig 1: Experimental setup for the hemodynamic study.

(6 SPD-rats for each vehicle)



AB=Acid-Base with pH, pCO2, pO2, BE, Hb, Na, K from 100 µl of blood

CALCULATIONS AND STATISTICS

Arterial blood pressure and heart rate data

The data for each animal (n=6 for all experiment except heart rate data for PEG 400 (50%) where n=5) were normalized using the mean of the first three data points as a baseline and the deviation from this baseline for each datapoint was calculated. The two vehicles were compared by calculating the mean difference between each vehicle (PEG 400 (50%) or microemulsion) and the control (saline). A 95% confidence interval using the pooled variances and the t-distribution compensated for consecutive measurements with the Bonferoni technique for the data points immediately after each infuson was calculated.

<u>ECG, acid-base balance, blood gases and plasma elecrolytes</u>

The results are presented as mean values and the variability is expressed as SEM (n=6).

RESULTS AND CONCLUSIONS

A microemulsion according to example 1a was compared with a 50% aqueous solution of PEG 400 which is a co-solvent often used for intravenous administration. Saline was used as a control. The results are shown i tables 1 - 3. The data shows that it is possible to administrate, by intravenous infusion to concious rats, a microemulsion according to example 1a up to 0.5 ml/kg without causing any significant effect on acid-base balance, blood gases, plasma electrolytes, , heart rate or PQ time. There is a significant but very small decrease in the arterial blood pressure immediately after the second dose but this is considered to be of no biological relevance.

At the highest dose, 1.5 ml/kg (microemulsion) and 3.0 ml/kg (PEG 400 (50%), the effect of the microemulsion and PEG 400 solution was very similar. A small increase in arterial blood pressure, for the microemulsion only, and a moderate bradycardic effect together with a temporary prolongation of the PQ time for both vehicles.

The solubility of felodipine and the indenoindol used in example 3 in PEG 400 (50%) are 0.7 mg/ml and 0.2 mg/ml respectively. Using the microemulsion it is thus possible to administrate 5 times more of felodipine and over 100 times more of the indenoindol compared to a 50% solution PEG 400. The microemulsion is surprisingly superior compared to The PEG 400 solution for solubilization and administration of compounds with a low solubility in water.

Table 1a. Arterial blood pressure (mm Hg)

Time(min)	-25.5	-15.5	-5.5	4.5	14.5	24.5	34.5	44.5	54.5	64.5	74.5	84.5	94.5	104.5	114.5	124.5	134.5	144.5
Peg 400-sal	-0.4	1.9	-2.7	0.8	1.2	4.7	2.2	-1.8	0.4	3.6	5.9	5.9	2.9	2.4	0.8	5.5	0.3	0.7
Conf. int.(95%)				+-6.0						+-10.4						+-10.6		
Microem.-sal	2.8	-1.2	-1.4	2.5	-1.7	5.3	6.2	-0.7	-0.3	6.6	3.6	4.5	4.3	1.4	4.1	13.0	3.5	8.9
Conf. int (95%)				+-5.3						+-8.6						+-8.7		

Table 1b. heart rate (beats/min)

Time(min)	-25.5	-15.5	-5.5	4.5	14.5	24.5	34.5	44.5	54.5	64.5	74.5	84.5	94.5	104.5	114.5	124.5	134.5	144.5
Peg 400-sal	0.2	13.7	3.2	-15.2	-2.5	11.3	2.7	-5.5	4.6	-20.3	4.3	-1.9	1.6	4.5	0.6	-43.7	-26.9	0.3
Conf. Int.(95%)				+-8.7						+-20.4						+-15.4		
Microem.-sal	8.0	7.0	6.9	-12.3	-10.1	21.9	20.9	-5.0	4.8	-24.7	-13.3	7.1	19.9	16.7	18.5	-36.9	-16.1	18.8
Conf. int (95%)				+-13.9						+-23.0						+-20.4		

Table 2. PQ-time (msec)

Time(min):	29	36	59	66	119	126	155
Saline:	45.8	43.7	45.3	45.5	46.0	45.1	47.0
SEM:	0.99	0.86	0.86	0.68	1.02	0.40	0.95
PEG 400 (50%):	45.3	45.3	44.7	46	44.2	51	46.3
	1.42	1.48	1.57	1.51	1.37	2.11	1.71
Microemulsion:	46.2	47.3	46.5	49	44.5	51	44.5
SEM:	1	0.68	1.04	0.98	1.1	1.77	0.81

Table 3. Acid-base balance, blood gases and plasma electrolytes.

	pH		pCO2 (kPa)		pO2 (kPa)		BE (mmol/L)		Na (mmol/L)		K (mmol/L)	
Time (min):	0	155	0	155	0	155	0	155	0	155	0	155
Saline	7.49	7.49	4.45	4.93	12.13	12.08	2.73	4.42	142.83	140.67	3.47	3.73
SEM	0.01	0.01	0.18	0.20	0.12	0.25	0.62	1.10	0.75	0.21	0.40	0.14
PEG 400 (50%)	7.47	7.47	4.37	4.39	11.93	12.06	0.83	0.85	143.67	142.83	3.00	3.07
SEM	0.01	0.01	0.09	0.10	0.24	0.35	0.59	0.56	0.88	0.70	0.14	0.15
Microemulsion	7.47	7.47	4.91	4.24	11.48	11.13	3.12	0.58	141.50	143.33	3.32	2.93
SEM	0.01	0.01	0.23	0.18	0.62	0.73	1.09	0.57	1.18	0.80	0.27	0.13

Claims

1. A non-toxic oil-in-water or bicontinous microemulsion as a vehicle for administration of one or more active compounds having a low solubility in water, which microemulsion contains

- a polar phase containing water and optionally an agent for obtaining isotonic conditions, and one or more components (modifiers) for adjusting the polarity of the polar phase,
- a surfactant film modifier,
- a non-polar phase consisiting of at least one pharmaceutically acceptable oil and
- a mixture of a hydrophilic surfactant and a hydrophobic surfactant up to 15% by weight of the total microemulsion, wherein the hydrophobic surfactant is chosen from a group consisting of lecithin, sphingolipids or galacto lipids.

2. A microemulsion according to claim 1 c h a r a c t e r i z e d in that the component for adjusting the polarity of the polar phase is one or more of

a) polyethylene glycol, i.e. polyethylene glycol 200, polyethylene glycol 300 or polyethylene glycol 400; propylene glycol; glucofurol; glycerol; or one or more of

b) sorbitol; mannitol; monosaccharides; disaccarides; or one or more of

c) dimethyl acetamide; solketal; methylpyrrolidone; 1-hydroxyethyl-2-pyrrolidon or hydroxyethyl lactamide.

3. A microemulsion according to claim 2 c h a r a c t e r i z e d in that the component for adjusting the polarity of the polar phase is one or more of

a) polyethylene glycol; propylene glycol; glucofurol; glycerol; or one or more of

b) sorbitol; mannitol; monosaccharides or disaccarides.

4. A microemulsion according to claim 2 and 3 c h a r a c t e r i z e d in that the component for adjusting the polarity of the polar phase is polyethylene glycol 400.

5. A microemulsion according to claim 1 c h a r a c t e r i z e d in that the agent for obtaining isotonic conditions is a solution of NaCl or glycerol.

6. A microemulsion according to claim 1 c h a r a c t e r i z e d in that the surfactant film modifier is an alcohol with 2-3 carbon atoms.

7. A microemulsion according to claim 6 c h a r a c t e r i z e d in that the surfactant film modifier is ethanol.

8. A microemulsion according to claim 1 c h a r a c t e r i z e d in that the pharmaceutically acceptable oil in the non-polar phase is a triglyceride containing 4-18 carbon atoms; a diester of propylene glycol containing fatty acids having 4-18 carbon atoms; a monoester of fatty acid containing an alcoholic part consisting of 1-5 carbon atoms or a fatty acid part having 8-22 carbon atoms, or mixtures thereof.

9. A microemulsion according to claim 8 c h a r a c t e r i z e d in that the pharmaceutically acceptable oil in the non-polar phase is a triglyceride containing at least 70 % of fatty acids having 8-10 carbon atoms; a diester of propylene glycol containing at least 70 % of fatty acids having 8-10 carbon atoms; a monoester such as isopropylmyristate, isopropylpalmitate, ethyloleate or mixtures thereof.

10. A microemulsion according to claim 9 c h a r a c t e r i z e d in that the pharmacutically acceptable oil in the non-polar phase is a triglyceride containing at least 70% of fatty acids having 8-10 carbon atoms; isopropylmyristate or mixture thereof.

11. A microemulsion according to claim 1 c h a r a c t e r i z e d in that the hydrophobic surfactant is purified soybean lecitin comprising at least 90 % phosphatidyl cholin.

12. A microemulsion according to claim 1 c h a r a c t e r i z e d in that the hydrophilic surfactant is ethoxylated castor oil; ethoxylated fatty esters; sucrose fatty esters; mono-, di-,

and triesters of sorbitol or sorbitan and polyethylene derivatives thereof; alkyl glucosides or alkyl polyglucosides; ethoxylated mono-hydroxy steric acid; bile salts or mixtures thereof.

13. A microemulsion according to claim 12 c h a r a c t e r i z e d in that the hydrophilic surfactant is polyethylene glycol(15)-12-hydroxy stearate, alkylmaltoside, bile salts or mixtures thereof.

14. A microemulsion according to claim 1 c h a r a c t e r i z e d in that the amount of surfactant is up to 15 % by weight of the total microemulsion.

15. A microemulsion according to claim 1 c h a r a c t e r i z e d in that the amount of surfactant is 4-12 % by weight of the total microemulsion.

16. A microemulsion according to claim 1 c h a r a c t e r i z e d in that it is an oil-in-water microemulsion.

17. A microemulsion according to claim 1 c h a r a c e t i z e d in that the active compound is a pharmaceutical.

18. A microemulsion according to claim 17 c h a r a c t e r i z e d in that the active compound is a proton pump inhibitor, calcium channel blocker, beta blocker, anesthetics, steroid, antioxidant, renin inhibitor, alkaloid, cytostatica, antocoagulant, lipid regulating agent, antidepressant, neuroleptic, immunosuppressant, immunomodulator, antibiotic or an antiinflammatory agent.

19. A process for the preparation of a microemulsion according to claim 1 c h a r a c t e r i z e d in mixing the components together in no particular order and allow the mixture to equilibrate typically one or two days, whereby the equilibrating procedure

could be shortened by gentle heating of the mixture, about 40°C, and stirring or shaking the mixture at regular intervals.

20. Use of a microemulsion according to any one of claims 1 - 18 for administering an effective amount of one or more active compounds to a host in need of such active compounds.

21. Use of a microemulsion according to claim 20 for parenteral administration of an effective amount of one or more active compounds to a host in need of such active compounds.

22. Use of a microemulsion according to claim 20 for oral administration of an effective amount of one or more active compounds to a host in need of such active compounds.

23. Use of a microemulsion according to claim 20 for transdermal administration of an effective amount of one or more active compounds to a host in need of such active compounds.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/01097

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/107
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EDOC, PAJ, PCI, USPATFULL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0334777 A1 (GATTEFOSSE S.A.), 27 Sept 1989 (27.09.89), column 2, line 56 - column 3, line 39, claim	1-23
	--	
X	EP 0391369 A2 (YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM), 10 October 1990 (10.10.90), see claims	1-23
	--	
A	EP 0651994 A1 (DIETL, HANS, DR.), 10 May 1995 (10.05.95)	1-23
	--	

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
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- "P" document published prior to the international filing date but later than the priority date claimed
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- "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 November 1996	29 -11- 1996
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Patrick Andersson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/10/96

International application No.
PCT/SE 96/01097

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP-A1-	0334777	27/09/89	DE-U-	6890156	25/06/92
			FR-A,B-	2628632	22/09/89
EP-A2-	0391369	10/10/90	AT-T-	110563	15/09/94
			AU-B-	614465	29/08/91
			AU-A-	5292790	11/10/90
			CA-A,C-	2013755	05/10/90
			DE-D,T-	69011922	12/01/95
			JP-A-	2290809	30/11/90
			JP-B-	7121857	25/12/95
			US-A-	5364632	15/11/94
			IL-A-	93558	27/11/95
EP-A1-	0651994	10/05/95	DE-A-	4338046	11/05/95